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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,894	07/06/2005	Braj B. Lohray	GRT/4062-127	1052

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/509,894	LOHRAY ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12 and 17* is/are rejected.

7)☒ Claim(s) *3,13-16 and 19-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/1/04 & 2/12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-17 & 19-21 are currently pending in the instant application; all of which are currently amended. **Claim 18** is canceled.

Priority

This application is a 371 of PCT/IN03/00133, filed on 04/01/2003. Receipt of 327MUM2002, filed on 04/05/2002 in India, submitted under 35 U.S.C. §§ 119(a)-(d) is acknowledged. Said papers have been placed of record in the file. Claim for priority in the specification is acknowledged.

Information Disclosure Statement

Applicants' information disclosure statements (IDS), filed on 02/12/2007 and 10/01/2004 have been considered. Please refer to Applicants' copies of the 1449 submitted herein. References where a line is drawn through have not been provided by Applicant or are repeated from another US form 1449.

Response to Restriction

Applicants' election with traverse of **Group II, Claims 1-17 & 19-21**, wherein **G** is a single heterocyclic group selected from the group consisting of **A-F**, is acknowledged. It is also acknowledged that Applicant agrees with Examiner in that the inventions identified by Examiner are separately patentable; however, traverses restriction requirement because the claims as originally filed would not constitute a serious burden.

Because unity of invention was lacking in the original claims, the restriction requirement is justified. Additionally, as originally presented, the claims pose a serious search burden on Examiner because the original claims, including G = aryl, represent a vast amount of prior art (over 10,000 compounds and 200 documents). Such a search is considered a serious burden, especially in light of the multiple inventions originally presented. The restriction is FINAL.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 & 4-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belley *et al.* (US Patent 6,020,343, 02/01/**2000**; see IDS), taken alone.

Determination of the scope and content of the prior art (MPEP § 2141.01)

The prior art teaches compounds, compositions and a method of making and using said compounds for the treatment of inflammation. The compounds of Formula I in Claim 1 of the '343 Patent are analogous to the compounds of the instant application wherein **G** = D, **Y** = O, and $\mathbf{R_3}$ = a substituted or unsubstituted alkyl. Although, Belley *et al.* have not published any species that anticipate the instant application, the broad teaching of this formula sufficiently suggests the compounds of the instant application outlined above.

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The differences between the prior art and instant application are of scope and are twofold: 1) the instant application is limited to a substituted "sulfamide" moiety, whereas the compounds taught in the '343 Patent include the group listed as $\mathbf{R_1}$ (a-g). The relevant $\mathbf{R_1}$ groups are (d) and (e) wherein the sulfur atom has a double bond to oxygen and nitrogen and is further substituted by $-NH_2$ or $-NHC(O)CF_3$; and 2) the instant application includes the other heterocyclic groups for **G**, whereas the '343 Patent is limited to only when **G** = D. Albeit the differences in scope, the instant application is suggested by the '343 Patent in Claims 1-4, 8, 18-20 & 36-37.

Finding of prima facie obviousness--rational and motivation (MPEP § 2142-2413)

The prior art teaches a broad genus. The instant compounds of formula (I) wherein **G** = D would be obvious to a skilled artisan because one would be motivated to prepare compounds embraced by the reference genus with the expectation that the obtained compounds would have the desired activity taught in the reference, (*In re Lemin* 141 USPQ 814). Examiner suggests canceling **G** = D.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 recites the limitation "R_3 and R_4 represent a cyano..." in the formula I of **Claim 1**. There is insufficient antecedent basis for this limitation in the claim. Examiner suggests the change from "R_3 and R_4" to "X_3 and X_4".

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 11 & 17 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for a method for the treatment of inflammation, does not reasonably provide enablement for the treatment of inflammatory-associated

disorders. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'."

In re Wands, 8 USPQ2d 1400 (1988), discusses the following factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph:

1. ***The nature of the invention;***
2. ***The state of the prior art;***
3. ***The predictability or lack thereof in the art;***
4. ***The amount of direction or guidance present;***
5. ***The presence or absence of working examples;***
6. ***The breadth of the claims;***
7. ***The quantity of experimentation needed; and***
8. ***The level of skill in the art***

each of which is discussed in turn below.

The nature of the invention

The nature of the invention is compounds and compositions of Formula I, the process for preparing these compounds, and methods of using these compounds.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities,

which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for inflammation, but it does not mean that the same group of compounds and compositions may provide treatment of any inflammatory-associated disorder. Listed in the specification (page 1, lines 16-21) are a diverse list of inflammatory-associated disorders, including cancer and Alzheimer's disease.

The amount of direction or guidance present and the presence or absence of working examples

The direction or guidance present in Applicants' Specification for a method of using the compounds and compositions of Formula I to treat inflammation is found on pages 1-4 (background of invention – inflammation), and on pages 31-40 (formulations, dose, and inhibitory activities).

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 9, 11 & 17 are drawn to "a method of treating inflammation or an inflammation-associated disorder." Inflammation is characterized by human redness, fever, swelling and pain; but inflammation-associated disorders include a number of diseases, including rheumatoid arthritis, osteoarthritis, pyrexia, asthma, bone resorption, cardiovascular diseases, dysmenorrheal, premature labor, nephritis, nephrosis, atherosclerosis, hypotension, shock, pain, cancer, and Alzheimer's disease. Inflammation may be a symptom of a certain cardiovascular disease or specific cancer, and the treatment of inflammation is supported within the scope of the invention; however, pathologically speaking, this is not the same as treating the disease itself. Furthermore, it is expected that different patient populations carry each of the disorders listed above. Therefore, because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. Examiner suggests amending **Claims 9, 11 & 17** to only treat inflammation.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds and compositions of the formula (I), including their pharmaceutically acceptable salts thereof; the specification is not enabled for their analogs, derivatives, and/or solvates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The Nature of the Invention

The nature of the invention is the compounds of formula (I), including all compositions, derivatives, analogs, pharmaceutically acceptable salts and solvates thereof. Examiner notes that there is no clear definition of what constitutes an analog or derivative; therefore, it is assumed that these terms can encompass polymorphs, etc.

The state of the prior art and the predictability or lack thereof in the art

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. APIs can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form

displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms such as polymorphs and solvates are not so common as to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials. A large number of factors can influence crystal nucleation and growth during this process, including the composition of the crystallization medium and the processes used to generate super-saturation and promote crystallization, (Morissette *et al.* Advanced Drug Delivery Reviews **2004**, *56*, 275-300).

For instance, the phenomenon of polymorphism, in the crystallization of organic compounds, is of crucial importance to the pharmaceutical industry. Two polymorphs of the same drug molecule may have different physical properties: e.g. solubility, bioavailability, melting points, density, hardness, or color; and may have dramatically different properties that effect the scale-up process. Due to the differences between polymorphs, the drug regulatory authorities (e.g. the FDA) are increasingly demanding more information about potential drug products before granting approval. The

conditions under which polymorphs interconvert is also of crucial importance, particularly when drugs may encounter exposure to changes in temperature, pressure, and relative humidity during processes such as drying, granulation, milling, compression, and storage. Therefore, for these reasons, the state of the prior art is one of unpredictability. The science of crystallization has evolved such that said differences in properties implies patentable distinctiveness between polymorphs.

Amount of direction/guidance & presence or absence of working examples

The direction or guidance present in the instant specification for the preparation of salts for the compounds of formula (I) is on page 31 (list of salts) and the examples in Table 16 on pages 72-74 of the specification. There are no working examples present in the disclosure for solvates, analogs or derivatives of formula (I). Therefore, one of skill in the art would be required to identify the correct solvent system and crystallization technique for each compound and, further, identify the similarities and differences between crystals and corresponding spectral data for each compound (polymorph) in order to determine what is being claimed.

The breadth of the claims

The instant breadth of the rejected claims is broader than the disclosure, specifically; the instant claims include any derivatives, analogs or solvates.

The quantity of experimentation necessary

While the level of the skill in the pharmaceutical arts is high, it would require undue experimentation of one of ordinary skill in the art to prepare *any* derivatives, analogs, polymorphs, or solvates of a compound of formula (I) as instantly claimed. The science of crystallization has evolved such that, without guidance or working examples for polymorphs in the specification, the claims lack enablement. This rejection can be overcome by deletion of the words: derivatives, analogs and solvates from **Claim 1**.

Claim Objections

Claims 3, 13-16 &19-21 are objected to as being dependent upon a rejected base **Claim 1**, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 21 is objected to because of the following informalities: on page 14, the pyridine structure is referred to as Group D, whereas it should be referred to as Group E, as in Claim 1 to maintain consistency. Appropriate correction is required.

Claim 21 is objected to under 37 CFR 1.75(c) as being in improper form because the term "all other symbols are as defined earlier" is not in a proper alternative form.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

REBECCA ANDERSON
PATENT EXAMINER

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Art Unit 1626

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Date: March 5, 2007